I. STATUS OF CLAIMS AND FORMAL MATTERS

Reconsideration and withdrawal of the rejections of the claimed invention is respectfully requested in view of the amendments, remarks and enclosures herewith, which place the application in condition for allowance.

With entry of this amendment, claims 1-14 would still be pending in this application. Claim 1 has been amended to incorporate the elements of previously considered claim 6 and claim 8. In addition, the concentration gradient range has been amended to the range of about 50% to about 60%. Support for this amendment can be found in the specification, e.g. paragraphs [0012] of the publication of the application and Examples 2 and 3. No new matter has been added by these amendments.

It is submitted that the claims, herewith and as originally presented, are patentably distinct over the prior art cited in the Office Action, and that these claims were in full compliance with the requirements of 35 U.S.C. § 112.

II. THE 35 U.S.C 103(a) REJECTION HAS BEEN OVERCOME

Claims 1-14 were rejected as allegedly being obvious Rupprecht et al. (US 2002-0142036 -"Rupprecht") in view of Levin (US 6,432,986 -"Levin"). The applicants request reconsideration in view of the above amendment and discussion below.

Rupprecht and Levin do not teach a monolayer

First, the combination of Rupprecht and Levin does not teach the element that the dosage form is a monolayer or that the monolayer is a film form comprising a lidocaine containing layer and that the lidocaine containing layer is also an adhesive layer.

Rupprecht and Levin do not teach the claimed concentration gradient

Second, the combination of Rupprecht and Levin does not teach that the concentration gradient of lidocaine is about 50% to about 60% by weight of lidocaine.

The state of the art is such that one of ordinary skill in the art would have been directed away from using such high dosages of lidocaine for a composition intended for nasal delivery, e.g. col. 4, line 13-21 of Levin stated that "[h]igh concentrations of lidocaine decreased head pain within fifteen minutes in 55% of the patients so treated. However, significant pain and

associated symptoms persisted in many of these patients following treatment. A significant number of patients required further treatment with other types of migraine medication to attain acceptable relief. Furthermore, the acute migraine episode frequently rebounded or relapsed early after treatment, usually within the first hour."

That Levin acknowledged such difficulties in working with lidocaine is not surprising given the state if the art regarding lidocaine. Some examples of the state of the art:

a. "Lidocaine is an antiarrythmic drug that is used only by the intravenous route." from Basic & Clinical Pharmacology, Seventh Ed., Appleton & Lange, page 232 (1998); "Because of its very extensive first-pass hepatic metabolism, only 3% of orally administered lidocaine appears in the plasma. Thus, ***lidocaine must be given parenterally***." (emphasis added) *Id.* @ 233.

b. "Toxicity. The side effects of lidocaine seen with increasing dose include drowsiness, tinnitus, dysgeusia, dizziness, and twitching. ***As the dose increases, seizures, coma, and respiratory depression and arrest will occur.*** Clinically significant cardiovascular depression usually occurs at serum lidocaine levels that produce marked CNS effects." (emphasis added) Goodman & Gilman's The Pharmaological Basis of Therapeutics (10th Ed.), pg. 375 (2001).

"Lidocaine (Xylocaine) is a local anesthetic that is also useful in the acute ***intravenous therapy*** of ventricular arrythmias. When lidocaine was administered to all patients with suspected myocardial infarction, the incidence of ventricular fibrillation was reduced...However, survival to hospital discharge tended to be decreased...perhaps because of lidocaine-exacerbated heart block or congestive heart failure. Lidocaine is therefore no longer routinely administered to all patients in coronary care units...Adverse effects. ***When a large intravenous does of lidocaine is administered rapidly, seizures can occur.*** When plasma concentrations of the drug rise slowly above the therapeutic range, as may occur during maintenance therapy, tremor, dysarthia, and altered levels of consciousness are more common. Nystagmus is an early sign of lidocaine toxicity." (emphasis added) *Id.* @ 961-962.

Not only does Levin not teach the concentrations of lidocaine claimed by the applicants, but Levin also does not teach that the administration can be achieved via a monolayer film form

dosage form. Levin refers only to administration via a cotton swab, nasal drops, nasal sprays or parenteral means (a syringe). As such, Levin does not suggest to one of ordinary skill in the art that intranasal administration of lidocaine with film forms such as those taught by Rupprecht would have been possible and actually teaches away from using such forms of administration.

Rupprecht and Levin do not teach intranasal delivery of lidocaine via a bioadhesive

Rupprecht is relied upon for a generic teaching with regard to transmucosal administration. However, there is no teaching or direction for this means of administration being nasal administration; the examples of Rupprecht are clearly directed toward oral transmucosal administration (see e.g. [0083] of Rupprecht).

If the position taken is that mucosal membranes are indistinguishable, this is clearly not true. For example, Allam et al., "Comparative analysis of nasal and oral mucosa dendritic cells", *Allergy* 61: 166-172 (2006) report on the likely phenotypic difference between the dendritic cell of nasal mucosa and oral mucosa which might result in diverse functional properties."

Moreover, Levin refers to intranasal administration via conventional means known in the art, i.e. via the use of a syringe (see e.g. Example 6 and Levin's reference to "dorsonasal" administration). There is no teaching by Levin which is directed toward intranasal administration via the use of a bioadhesive composition which would facilitate nasal transmucosal delivery of the drug.

As such, one of ordinary skill in the art would not have a reasonable expectation of success that a means of delivery intended for oral transmucosal administration would be applicable for nasal transmucosal administration.

Rupprecht and Levin do not teach the requisite combination of tear strength and lidocaine concentration suitable for intranasal delivery

As noted in the applicants' background section[1], the state of the art of lidocaine in high dosage amounts was not expected because other film-forming polymers such as ethylcellulose allow for a loading of only up to 25%. Active ingredient above this amount typically led to crystallization of the lidocaine and hence made it unsuitable for intranasal use. High loading also led to a brittle film which was unsuitable for intranasal use.

In addition, loading of lidocaine at higher concentration levels was not recommended by those of skill in the art because of the problems with toxicity as described above (see further, "Lidocaine Safety" section of *A Guidance on the Use of Topical Anesthetics for Naso/Oropharyngeal and Laryngotracheal Procedures*, VHA Pharmacy Benefits Management Strategic Healthcare Group and the Medical Advisory Panel and the National Center for Patient Safety, pgs. 10-11 (2006)("The toxicity of lidocaine has been extensively documented such that levels greater than 5ncg/mL are associated with increased toxicity. Serum lidocaine levels between 6 and 10 mcg/mL are associated with visual disturbances, muscle twitching, unconsciousness and seizures. Serum levels of approximately 15 mcg/mL have been associated with coma, and serum levels >20 mcg/mL are associated with cardio and respiratory arrest.")

For these reasons, one of ordinary skill in the art traditionally sticks to the conventional means of administering lidocaine, e.g. use of topical solutions, viscous solutions, jellies or ointments or administer via parenteral (injection) means.

Moreover, there is no recognition by Rupprecht and Levin that a combination of high lidocaine concentration could be achieved simultaneously in a monolayer dosage form with a tear strength of over 40 N, i.e. having high concentration of lidocaine and being suitable for insertion of the dosage form into the nose and ultimately removal of the dosage form from the nose.

The lidocaine released from an embodiment of the claimed invention is depicted in Figure 1. It can bee seen from Figure 1 that the release of lidocaine and therefore, the action of lidocaine, can be extended to ***at least five hours*** of anesthetic/analgesic effect which is a surprising and unexpected result in view of the combined teachings of Rupprecht and Levin.

In contrast, Rupprecht teaches no such effect, concentration or suitability to insertion and removal of the dosage form from the nose. Likewise, Levin is directed toward intranasal administration and refers to lidocaine exhibiting a duration of action ***shorter than about one hour*** when intranasally administered (see col. 11, lines 26-28 of Levin). Levin's methods do nothing to improve upon the state of the art with respect to extending the time period of providing an anesthetic or analgesic effect.

At best, Levin merely discovered that "anesthesia of a dorsonasal nerve structure (DnNS) in a human patient experiencing a CNvD (cerebral neurovascular disorder) inhibits the CNvD or

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[1] see paragraph [0011] of the publication of the application

a symptom of the CNvD if the anesthesia persists for a period of at least about an hour, and preferably for a period of at least about two hours."

Therefore, the applicants' claims as amended are not rendered obvious by the combination of Rupprecht and Levin because the combination of these references do not suggest all elements of the applicants claimed invention or that the bioadhesive pharmaceutical dosage forms such as those claimed by the applicants could be made to extend the anesthetic/analgesic effect far beyond what had previously been known in the art for intranasal administration.

IV. CONCLUSION

In view of the remarks and amendments herewith, the application is believed to be in condition for allowance. Favorable reconsideration of the application and prompt issuance of a Notice of Allowance are earnestly solicited. The undersigned looks forward to hearing favorably from the Examiner at an early date, and, the Examiner is invited to telephonically contact the undersigned to advance prosecution. The Commission is authorized to charge any fee occasioned by this paper, or credit any overpayment of such fees, to Deposit Account No. 50-0320.

Respectfully submitted,
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Goodman & Gilman's The Pharmaological Basis of Therapeutics (10th Ed.), pg. 375, 961-962 (2001).

Allam et al., "Comparative analysis of nasal and oral mucosa dendritic cells", *Allergy*, pgs. 166-172 (2006).

"Lidocaine Safety" section of *A Guidance on the Use of Topical Anesthetics for Naso/Oropharyngeal and Laryngotracheal Procedures*, VHA Pharmacy Benefits Management Strategic Healthcare Group and the Medical Advisory Panel and the National Center for Patient Safety, pgs. 10-11 (2006).